A New Millennium for Inhaler Technology

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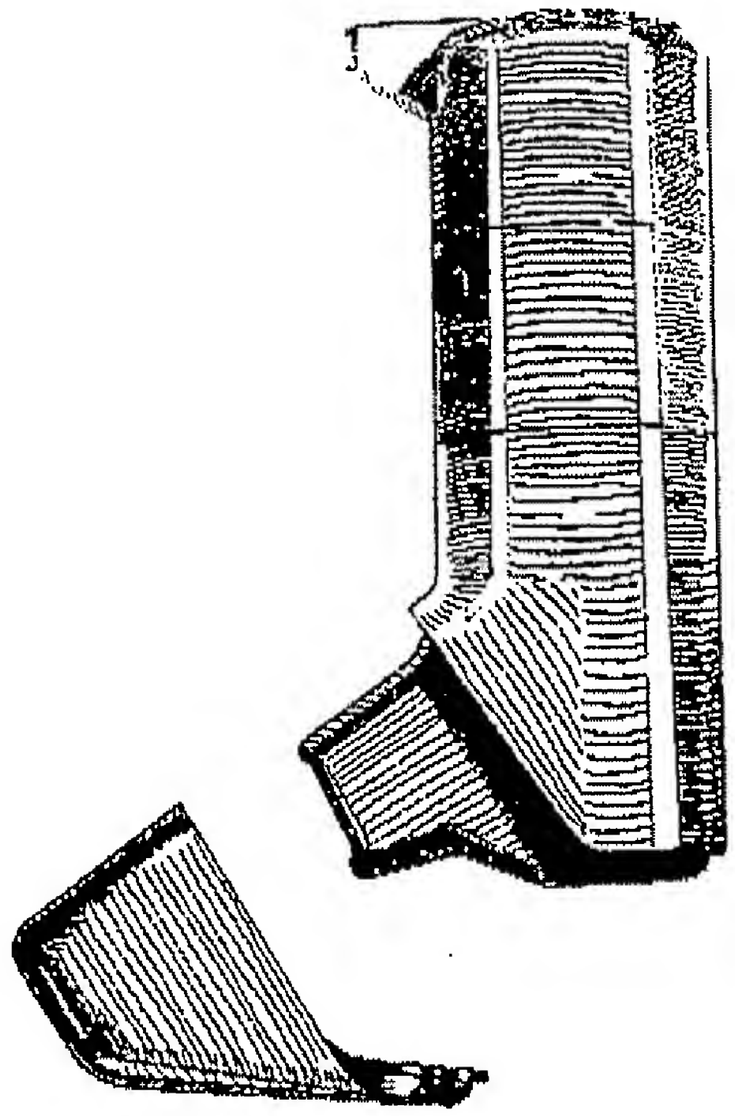

In recent years dramatic developments have occurred in the technology associated with aerosol delivery of drugs to the lungs. Propellant-based metered-dose inhalers have entered a new phase in which chlorofluorocarbons have been joined by so-called environmentally friendly propellants as a means of aerosol propulsion. Active emission dry powder inhalers have been manufactured, and may supersede those based on the passive inspiratory flow of the patient. Self-contained, hand-held, aqueous spray systems are being introduced and are capable of competing with metered-dose inhalers and dry powder inhalers. The current status of pharmaceutical inhalation aerosol technology indicates a bright future for drug delivery to the lungs, not only as the site of action but also as a route of administration.

The development of the first pressurized metered-dose inhaler (pMDI) for asthma therapy (Riker Laboratories, 1956) was a major advance in the use of aerosols for drug delivery to the lungs (1). Chlorofluorocarbon (CFC) propellants were used to disperse drug particles or droplets from the inhalers in sizes suitable for lung deposition. The metering of a nominal drug dose by a novel valve developed by Meshberg was central to the success of this device (2). Currently, the pMDI is the most frequently prescribed inhaler for the treatment of asthma. However, it is under increasing scrutiny because of the postulated contribution of CFCs to ozone depletion and global warming (3). Reformulation using so-called ozone-friendly propellants is the only alternative approach based on retaining pMDI technology. In response to the limited number of acceptable CFC propellants and reformulation opportunities, alternative devices to the pMDI have been given greater consideration. The number of research reports and patents describing the performance of dry powder inhalers (DPIs) indicate their leading position as a truly alternative technology. Conventional nebulizers are effective devices in terms of droplet dispersion and delivery to the peripheral regions of the lung, but they are not as portable as the other systems described above and are not popular for use outside the home or hospital. However, formulators are developing a new generation of hand-held, portable devices that will extend the use of aqueous aerosols as an alternative to pMDIs and DPIs.

In the 40 years since the development of the first pressurized packaged MDIs, the possibility of using the lung as a target route of administration for medicines has increased dramatically. The pages of *Pharmaceutical Technology* have often

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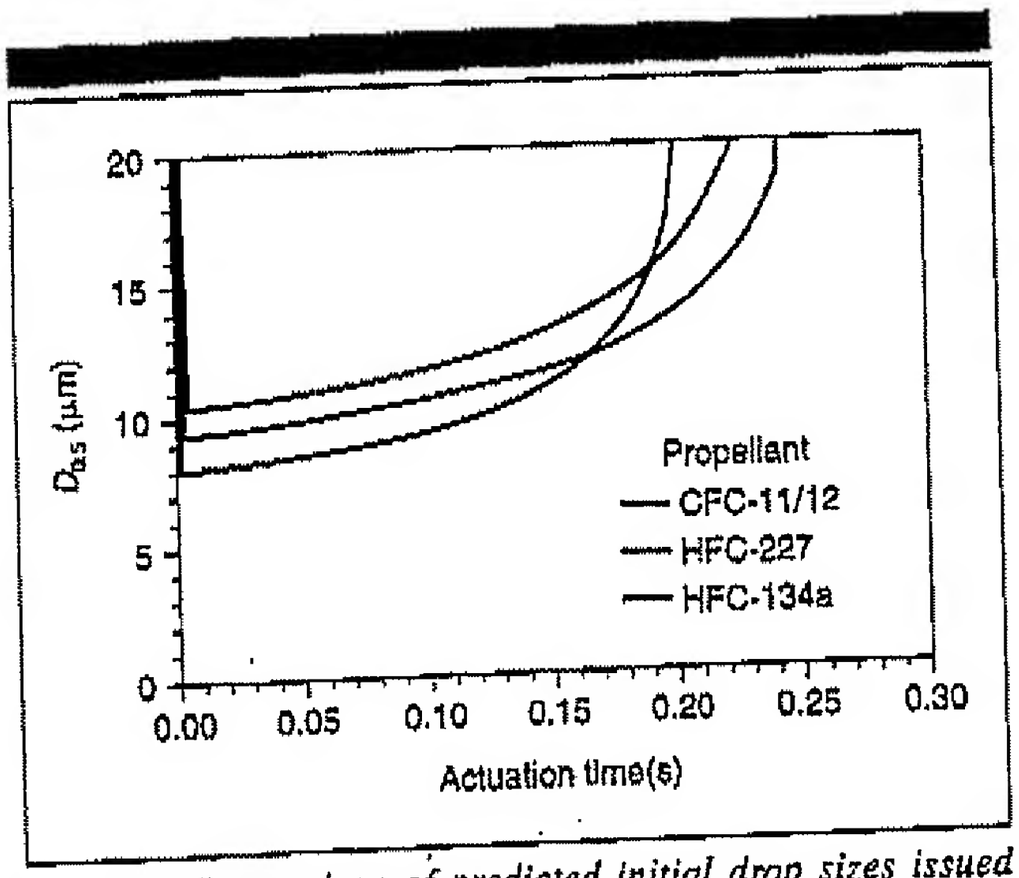

Figure 1: *Comparison of predicted initial drop sizes issued from a pMDI for various propellants.*

flected the state of the art or current debates regarding the means of delivery and characterization of these systems. The following overview addresses the role of various devices in the treatment of respiratory diseases and considers their future contributions to drug delivery to and via the respiratory tract. Methods of particle-size characterization are presented as this has been a topic of some debate in the past decade.

PRESSURIZED METERED-DOSE INHALERS

The pressurized metered-dose inhaler offers the most convenient, versatile, and cost-effective means of aerosol drug delivery available commercially. The device typically discharges more than 200 doses, producing a respirable spray of finely dispersed drug. The primary component of the pMDI is the formulation, the other components being the metering valve, actuator, and container.

The formulation most frequently consists of micronized drug particles suspended in a combination of propellants. Solution formulations are also available, but they represent a small proportion of the pressure-packaged aerosol market. Propellant blends have traditionally been a combination of chlorofluorocarbons (CFC-12, 11, and 114) providing the energy for atomization by virtue of their vapor pressure and leading to the production of respirable droplets. These propellants also have the important pharmaceutical characteristics of low toxicity, chemical stability, low cost, and good organoleptic properties.

Molina and Rowland first suggested in 1974 that the decomposition of CFCs by ultraviolet radiation in the upper atmosphere could lead to a build-up of chlorine and subsequent depletion of stratospheric ozone by the formation of chlorine monoxide (4). This was confirmed in 1985 with the discovery of an ozone hole in the atmosphere above Antarctica (5). The Montreal Protocol initiated international agreement leading to a ban on the production of all CFCs from the beginning of 1995 (6,7). As part of the effort to prevent further ozone depletion, the pharmaceutical industry responded by attempting to rapidly reformulate their pMDI devices with environmentally friendly propellants. It is not yet clear that all pMDI formulations can be reformulated in alternative propellants. Intermediate solutions to the reformulation problems have been suggested (8,9). Consequently, CFC propellants are expected to be retained for delivery of some compounds for the foreseeable future.

Open discussions of the reformulation issues for pMDIs between propellant manufacturers, the pharmaceutical industry, and academicians were a prelude to an "essential use" exemption and recognition of the complexities of reformulation (10,11). The situation will be reviewed in the near future, depending on the successful reformulation of pMDI products and the necessary approval by regulatory authorities. Formulation of albuterol in an alternative propellant (Airomir; 3M Pharmaceuticals, St Paul, MN), currently marketed in the European Union and the United States, may well have a direct impact on the future of CFC propellant–based products.

The alternative propellant candidates that have been assessed for toxicological approval are hydrofluorocarbons (HFCs) 134a and 227. The use of alternative propellants depends upon their ability to disperse droplets or particles in similar or smaller sizes than are generated by the current CFC products. Figure 1 shows the predicted mass median diameters ($D_{0.5}$) produced at the exit of the pMDI actuator for each prospective alternative propellant using an actuator flow model (12). These results are compared with the drop sizes produced by a traditional CFC-11/12 (28:72% w/w) propellant combination delivered via a 63-µL DF60 metering valve (Perfect Valois, Greenwich, CT). The results predict that the alternative propellants produce smaller initial drop sizes than do the CFC-based propellants and therefore can be considered as suitable replacements. Reformulation of pMDIs has required modification of metering valve design and development of new surfactants and cosolvents. As these technical difficulties are addressed, a number of alternative propellant devices will likely be available.

One of the most significant drawbacks of the pMDI has been patient coordination at the correct point in the inspiratory effort. Pediatric and elderly patients are most susceptible to the problems of device coordination. This is now being overcome with the introduction of breath-actuated devices such as the Autohaler (3M Pharmaceuticals, St Paul, MN) shown in Figure 2a. This device incorporates a diaphragm that actuates the pMDI at a given inspiratory pressure, thus negating the need for hand–inspiration coordination by the patient. More "intelligent" devices are being developed. SmartMist (Aradigm, Hayward, CA), shown in Figure 2b, is a hand-held device that integrates breath-actuation capabilities, a miniature pneumotachograph, and microprocessor so that a drug bolus can be delivered at a preprogrammed point in the inhalation cycle. Such devices will certainly have a role to play in future pMDI development.

DRY POWDER INHALERS

Dry powder inhalers are of increasing interest for the delivery of drugs to the lungs. The basis of aerosol delivery by these systems is the combination of the powder product, the metering system, and the method of dispersion, The first system for the delivery of dry powder drugs in modern times was the Spinhaler (Fisons, Rochester, NY) (13). This system has a unique dispersion mechanism that combines rotation with vibration to aerosolize the aerosol (14).

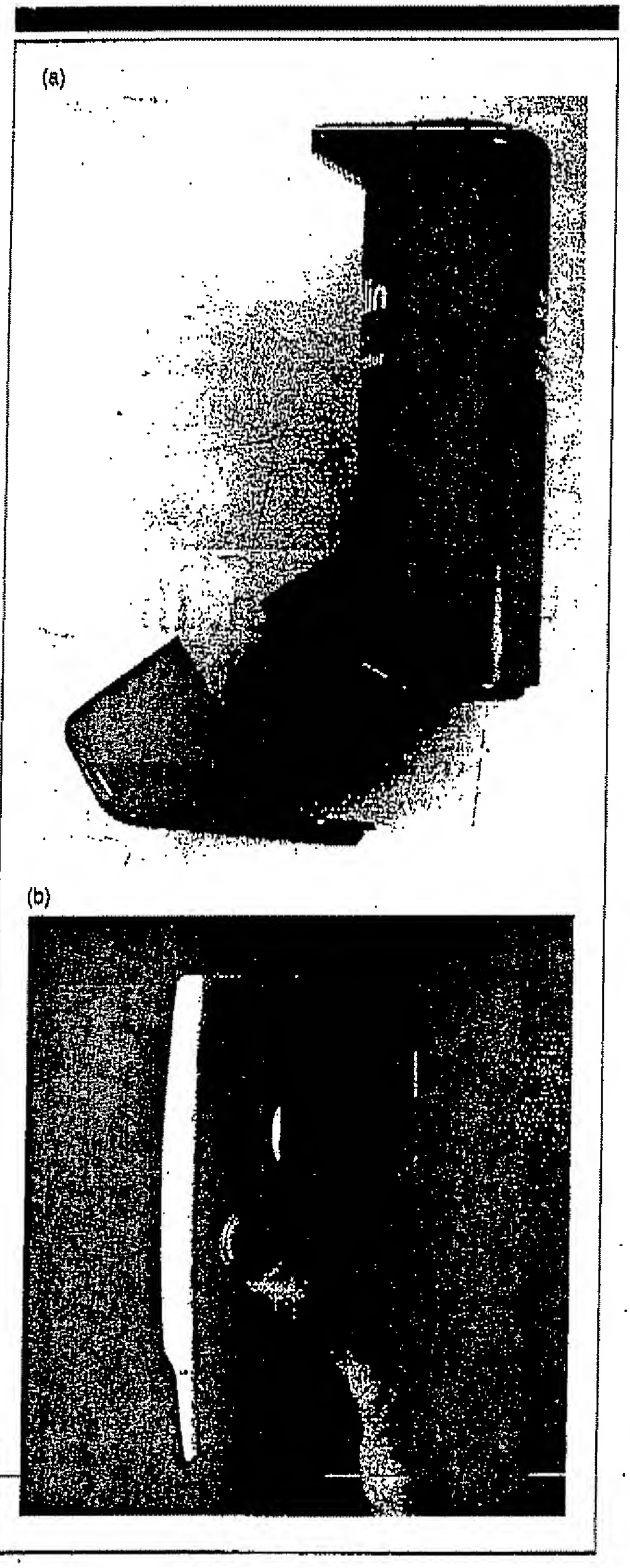

Figure 2: *Examples of breath-actuated and microprocessor-controlled pMDI devices: (a) Autohaler (3M Pharmaceuticals) and (b) SmartMist (Aradigm).*

In general, the powder product may consist of drug alone or blended with excipient (e.g., lactose). The excipient acts as a carrier with a size range of 30–60 μm, which is much larger than that required (<5 μm) for delivery to the lung (15). These carrier particles aid in the dispersion of the drug. The ease of dispersion of drug particles relates to their particle size and distribution, morphology, and surface characteristics. These are related to the forces of interaction between particles (16). A number of studies of basic powder properties and turbulent flow have been performed (17,18). However, further investigation may also be required for dry powder inhalers to fulfill their potential as alternatives to the pMDI (19).

The metering systems used in DPIs include hard gelatin capsule unit doses (Spincaps; Fisons, Rochester, NY, and Rotahaler; Glaxo Wellcome, Research Triangle Park, NC); blister packaged multiple unit doses (Diskhaler; Glaxo Wellcome, Research Triangle Park, NC) and reservoir systems (Turbuhaler; Astra, Lund, Sweden). The stability of the powder in these systems must be considered during the formulation process. Moisture ingress is a major source of both physical and chemical instability (20). It is often necessary to include desiccants to remove water from the immediate environment of the powdered drug.

The method of dispersion of commercially available products is passive inhalation (Spinhaler, Rotahaler, Diskhaler, and Diskus; Glaxo Wellcome, Research Triangle Park, NC, and Turbuhaler and Inhalator; Boehringer Ingelheim, Ridgefield, CT). This has the advantage of the drug source being dispersed by the patients' own inspiratory effort; its disadvantage is requiring the patient's optimum inhalation flow rate to effectively disperse the powder (21). Products currently under development use active dispersion mechanisms, for example, Spiros (Dura, San Diego, CA) and the Inhale Deep Pulmonary Drug Delivery System (Inhale, Palo Alto, CA). These devices are shown in Figures 3a and 3b, respectively. They offer the advantage that aerosol generation is independent of the patient's inspiratory flow. Thus, optimal lung deposition and therapeutic effect are achieved.

Pharmaceutical dry powders for lung delivery are commonly manufactured by jet milling and spray drying. Jet milling reduces the size of particles by attrition using high-velocity opposing air jets (22). Spray drying produces a dry powder by controlled evaporation of an atomized solution (23). Each of these manufacturing techniques produces particles with different characteristics that can alter the dispersion properties of the bulk powder.

A current area of interest in the production of respirable particles is supercritical fluid manufacture. This is a controlled crystallization technique in which the supercritical fluid can be presented as either a solvent or antisolvent (23–29). The advantage of supercritical fluid manufacture in the production of pharmaceutical powders is the elimination of the high-energy processes (attrition and heat transfer) that might damage the product (e.g., by denaturation of proteins or other labile molecules). This technique is known to produce particles of uniform size and morphology, which are attractive characteristics for aerosol delivery.

NEBULIZERS

Nebulizers offer the simplest and most effective means of droplet delivery to the peripheral regions of the lung. The principles used in nebulization of aqueous droplets fall into two categories: airblast and ultrasonic aerosol generation. Airblast nebulizers work on the principle that a high-pressure air jet produces a local pressure drop, thus drawing the fluid in

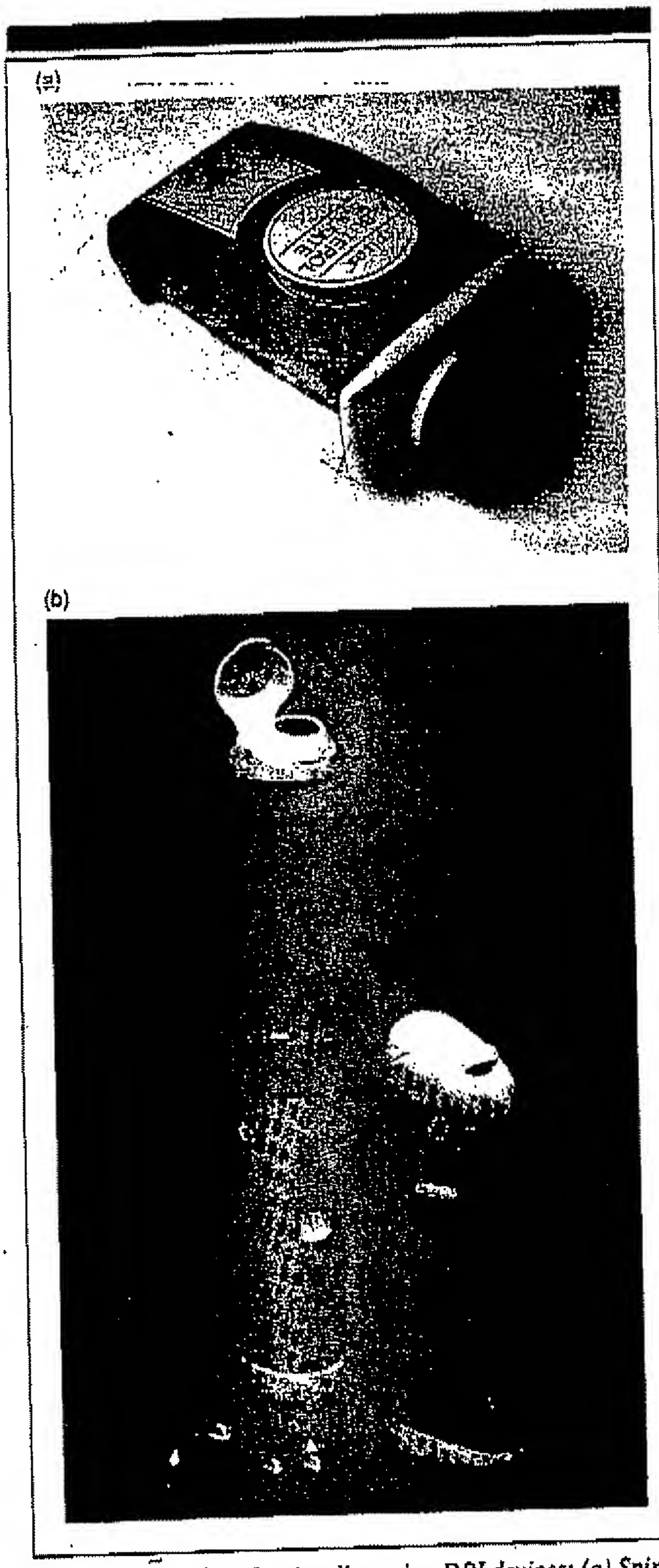

Figure 3: *Examples of active dispersion DPI devices: (a) Spiros (Dura) and (b) Inhale deep pulmonary drug delivery system (Inhale).*

airstream by capillary action. The fine liquid stream is then disintegrated by shear forces. Ultrasonic nebulizers work by imposing a rapidly oscillating waveform onto a liquid film via an electromechanical vibrating surface. At a given amplitude the waveform becomes unstable, disintegrating the liquid film and producing small droplets.

An advantage of the nebulizer is the relative ease of formulating aqueous solutions. In the past, the principal drawback of the nebulizer was its lack of mobility because it required a compressed gas source (airblast) or electrical power unit (ultrasonic). A convenient and portable vibrating aperture nebulizer that uses a small electrical power unit (shown in Figure 4) is currently under development (Aerogen, Santa Clara, CA). This may be the first step toward a new generation of nebulizers.

One exciting prospect that has been in development during the past 5 years is that of a truly portable, hand-held nebulizer that will deliver aqueous solutions complementing the powder and pressure-packaged devices. Two new systems, the BiNeb (Boehringer Ingelheim, Ingelheim am Rhein, Germany) and AERx (Aradigm, Hayward, CA), operate on different principles that allow a single-unit dose of drug to be administered. The BiNeb consists of a nozzle that has two coincident outlet channels (~8 µm) through which the liquid dose is accelerated, resulting in impaction of the two streams and atomization. The energy for atomization is provided by a compressed spring and metering pump (30). AERx is based on the principle of a unit-dose disposable blister pack (31). A mechanical actuator forces the liquid dose in the blister container through a multiorifice nozzle, producing an aerosol (32). A heating element is provided to control the relative humidity of the inhaled air, and it includes microprocessor-controlled delivery technology, similar to that of the SmartMist.

CHARACTERIZATION METHODS

Particle-size characterization of respirable aerosols has been the subject of much discussion because of the requirement of in vitro testing and the tendency to extrapolate data to lung deposition. Methods for characterizing inhalation aerosols are diverse. They have been reviewed by the Particle Size Subcommittee of the AAPS Aerosol Group and include impinger methods, cascade impaction, laser diffraction, time-of-flight aerosol beam spectrometry, holography, microscopy, right-angle light scattering, and phase-Doppler particle analysis (33–40).

The primary method for aerosol characterization is inertial impaction, which provides information on the aerodynamic particle size and distribution by inertial differentiation of particles. A number of pharmacopeias have adopted this method. The value of inertial impaction lies in its ability to provide information on drug content of the whole aerosol, along with particle size and distribution.

Inertial impactors provide quantitative data on device performance that are extremely useful in setting product specifications but are often interpreted in terms of the potential for lung deposition. After considerable debate, discussion continues on the legitimacy of some interpretations of impaction data. Most of this discussion focuses on selection of cutoff diameters to define the aerosol distributions, representative sampling flow rates, and sampling inlet geometries. One interesting observation is that the human throat exhibits a broad cutoff collection efficiency across a range of particle diameters (41). This is illustrated in Figure 5, which shows the retention efficiency of the throat predicted by a semiempirical model for an average inspiratory flow rate of 64.5 L/min (42). The two-stage liquid impinger follows a broad cutoff collection efficiency, as shown by the calibration curve in Figure 5 for a flow rate of 60 L/min (the retention efficiency curve similar to the one obtained

mentally has been predicted using computational fluid dynamics (CFD), also shown in Figure 5 (43,44). Thus, under these defined conditions the collection efficiency of the two-stage liquid impinger could be considered similar to the deposition characteristics in the oropharynx. The concept of the head as a blunt sampling inlet is not novel, and it is possible to design impactors to approximate a predetermined deposition curve (45,46). Nevertheless, anyone interested in the lung deposition of aerosols is referred to direct studies of this phenomenon. Radioisotopes may be used to quantify lung deposition, and predictive therapeutic models have been developed (47,48).

It is essential for thorough characterization that methods must not oversimplify the description of the aerosol. The complex interactions occurring within an aerosol may require a knowledge of the particle-size distribution; location of the drug; velocity of the emitted particles or droplets; fluid flow, heat, and mass transfer rates; and plume dimensions. The uncoupling of these interactions can lead to exhaustive experimental designs, and for this reason there may well be a role for computational modeling of the aerosol to provide an insight into areas that are difficult to delineate experimentally.

Standard methods of particle-size analysis for pMDIs and DPIs are being developed (49–51). In contrast, standard testing procedures have not been specified to evaluate nebulizer performance. The nebulizer has a number of components (e.g., reservoir, outlet, tubing, and mouthpiece/face mask); therefore, the definition of a benchmark nebulizer system is required because modifications in any of these parameters can significantly alter the estimated output characteristics (52). A system of this nature should be accompanied by definitions of standard operating conditions including airflow rates, adaptors, sampling tubes, and sampling times.

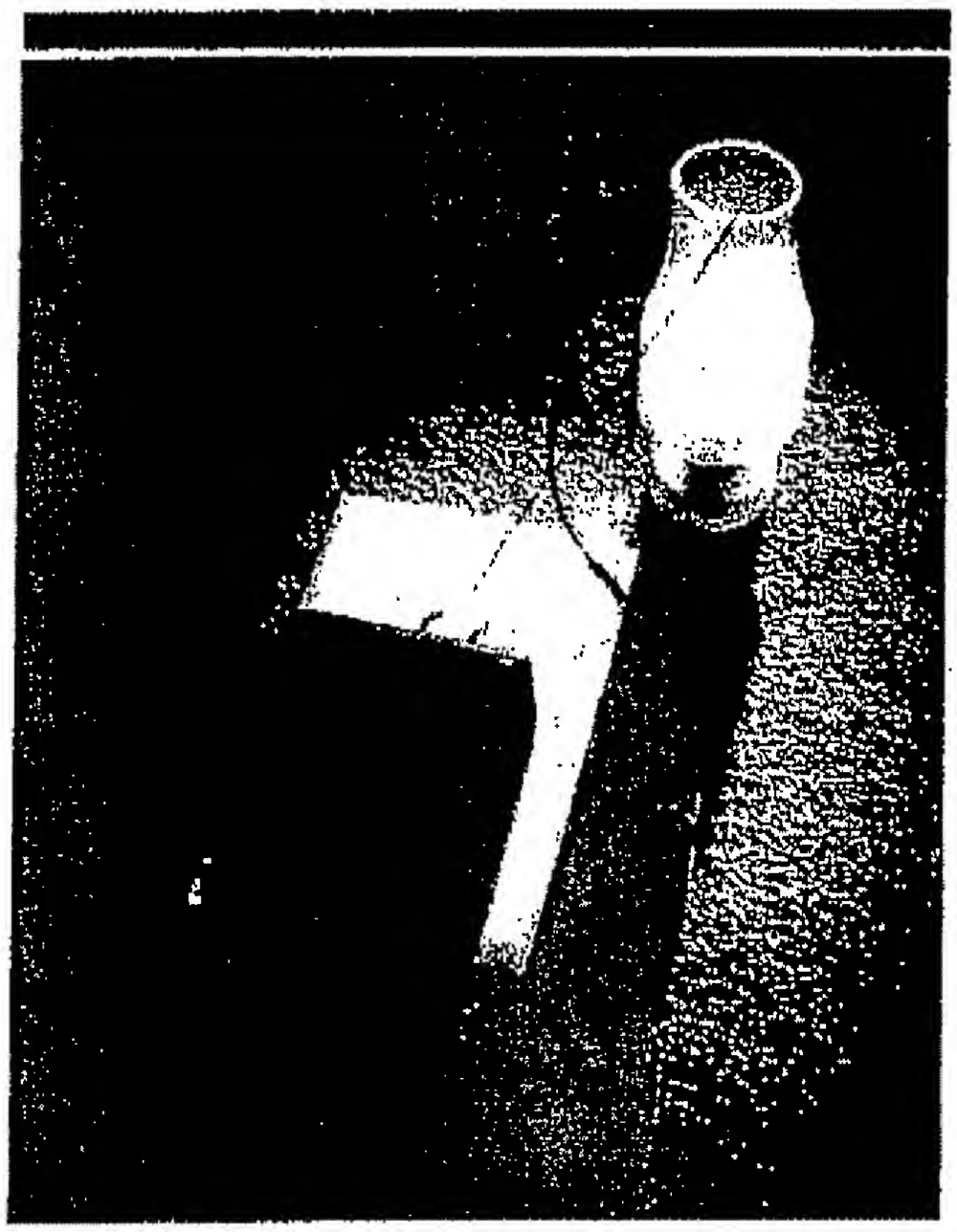

Figure 4: *Aerogen portable nebulizer (Aerogen).*

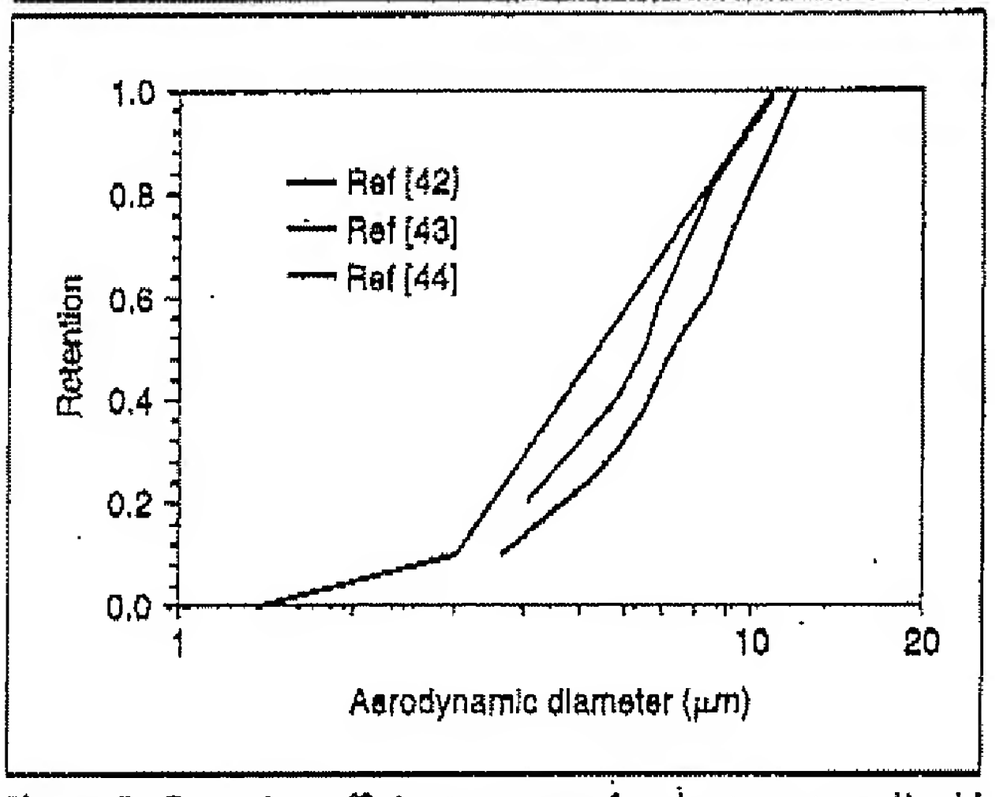

Figure 5: *Retention efficiency curves for the two-stage liquid impinger and predicted oropharyngeal deposition (42–44).*

CONCLUSION

Many exciting developments have taken place in the technology associated with the delivery of medicinal aerosols. The Montreal Protocol brought about an irreversible change in the approach to research and development of inhalers, directly for the pMDI and indirectly for both the DPI and nebulizers (6). Multiple issues are now being addressed to improve these delivery systems in areas that were considered satisfactory before the introduction of the Montreal Protocol. Investigations into the basic mechanisms of pMDI spray production, the development of new technologies, and approaches to device development are now taking the propellant-driven inhaler into the 21st century (53–55). The same is true of the DPI, as the mechanisms of powder dispersion are better understood (14,16), along with the development of more exotic formulations and novel devices. Nebulizers will have a role to play in the future as technology transforms the device into a compact, self-contained aerosol delivery device.

New devices may be designed to satisfy patients' needs. Feedback into the design process with regard to the practical and esthetic aspects of the inhalers may become commonplace, thus making them simple to use, and capable of monitoring and modifying therapy by collating information on usage (e.g., counters, pulmonary function testing, etc.) (56). Aerosol formulations containing proteins, peptides, and nucleic acids for local and systemic therapy are already under development in parallel with novel devices for their delivery (57). However, significant challenges need to be overcome in this area, including formulation development to establish a general understanding of the complex interactions of proteins and peptides with propellants and additives, as well as degradation during manufacture, storage, and delivery (58).

Pharmaceutical Technology has always been an open forum for presentation of current and novel concepts in aerosol delivery. It will continue to be a useful medium through which to

encourage discussion and communicate information to the pharmaceutical community on new developments in the field of inhalation aerosol technology.

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NEWS BRIEF

Pump efficiency video available from DOE

The US Department of Energy (DOE) and the Hydraulic Institute (HI), a trade association of pump manufacturers, have created an educational video to promote energy efficiency in electrically powered pumping systems.

According to DOE, pumps and pumping systems account for more than 5% of the total energy used in the United States. The savings potential based on educating and training pump users and engineering contractors in the selection and use of pumps is estimated at 20%.

The video identifies specific opportunities for energy savings and explains the calculations and adjustments necessary to achieve higher efficiency. The hour-long program provides information regarding pump systems design, evaluation of performance characteristics, avoidance of excessive capacity and total head margins, and the use of multiple pumps and recovery turbines.

Production of the video was funded by DOE's Motor Challenge Program, an industry and government partnership designed to help industry save 5 billion kWh of electricity annually by 2000. The Motor Challenge promotes industrial energy efficiency through the use of efficient electric motors, drives, and driven equipment, and effective electric motor-driven system integration and optimization.

For further information on the DOE/HI video program, the Motor Challenge program, or to obtain the pump efficiency video and materials, contact the Motor Challenge Clearinghouse at 1301 Clay St., Oakland, CA 94612, tel. (800) 862-2086.